

Progressive Ataxia of Unknown Etiology

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Introduction

The hereditary ataxias are a heterogeneous group of diseases. Most attempts at classification have been based on pathologic findings and are not always useful for the clinicians. Many of these disorders are multisystem degeneration in which the underlying biochemical or other defect is usually unknown. The pathophysiology is correspondingly poorly understood. Hereditary ataxia can be divided into the hereditary congenital ataxia, the ataxia linked with metabolic disorder, and early onset ataxia of unknown etiology (1) (Table 1).

Table 1: Classification of Hereditary Ataxia

I.	Congenital Cerebellar Ataxia
II.	Ataxia associated with metabolic disorders
	a. Intermittent ataxia syndromes
	b. Progressive unremitting ataxia syndromes
	c. Ataxia disorders associated with defective DNA repairs
III.	Progressive ataxia disorders of unknown etiology.
	a. Early - onset cerebellar ataxia (onset usually before age 20)
	b. Late - onset cerebellar ataxia (onset usually after age 20)

Classification

The degenerative cerebellar and spinocerebellar disorders are a complex group of diseases, most of which are genetically determined. Tremendous confusion exists in classifying degenerative disorders causing ataxia, and there is no universally accepted system. These disorders can be divided into two main groups, depending on whether onset of symptoms is before or after the age of 20 years. Most of the early onset are autosomal recessive, and the later onset ones autosomal dominant (2). Most of these disorders are multisystem degenerations in which the underlying biochemical or other defect is usually unknown; the pathophysiology is correspondingly poorly understood. The differential diagnosis of ataxia is important since some of them are treatable if detected early. The discussion will concentrate on progressive ataxia of unknown etiology.

Progressive Ataxia Disorders of Unknown Etiology

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A. Early Onset Cerebellar Ataxia

Friedreich's ataxia (FA)

Friedreich's ataxia is the most common of the early onset ataxia. It is one of the best defined and most common forms of hereditary ataxias of unknown etiology(1,2). In some large case series it comprises about 50% of the hereditary ataxia (2,3). It is transmitted in an autosomal recessive manner, with occasional sporadic cases, and usually appearing in childhood or in adolescence but rarely in old age (4). The disease usually progresses slowly without remission, affecting both the central and peripheral nervous system (4,5). The most frequent first symptom is ataxia of gait, although occasionally scoliosis or cardiac symptoms precede definite neurologic symptoms.

The epidemiology of Friedreich's ataxia is perplexing. The clinical features and diagnostic criteria were defined by the Quebec Cooperative Study of Friedreich's Ataxia (QCSFA) (6) and by Harding (1,2) (Table 2). Both authors regarded recessive inheritance, progressive ataxia of limbs and gait and lower limb areflexia as obligatory criteria. The onset, according to the QCSFA and Harding (2, 6), should never occur after the age of 20 years, and always before 25, according to Harding (2). A recent case was reported in the literature where symptoms started at a later stage (7). Both consider extensor plantar response, pes cavus, scoliosis and cardiomyopathy frequent, but not essential signs. Dysarthria, decreased lower limb deep sensation and weakness, obligatory signs for the QCSFA, are not considered essential for an early diagnosis by Harding (2). The diagnosis is made essentially on clinical grounds; CT scan of the brain may show mild cerebellar atrophy.

Table 2: FRIEDREICH'S ATAXIA : DIAGNOSTIC CRITERIA

Essential Criteria for Diagnosis: Present in More than 95% of Cases

Autosomal recessive inheritance
 Age at onset of symptoms before 25 y
 Progressive limb and gait ataxia
 Absent knee and ankle jerks
 Extensor plantar responses
 Motor nerve conduction velocity > 40m/s in upper limbs
 Small or undetectable sensory action potentials

Additional Criteria, Not Essential for Diagnosis: Present in More than 65% of Cases

Dysarthria*
 Pyramidal weakness of lower limbs
 Absent reflexes in upper limbs*
 Distal loss of joint position and vibration sense in lower limbs*
 Scoliosis
 Abnormal electrocardiogram

Other Features Present in 50% of cases or less

Nystagmus
 Optic atrophy
 Deafness
 Distal weakness and wasting
 Pes cavus
 Diabetes

The prevalence is known only for some populations (3, 8-11). The range is from 0.6 to 1.4/100,000 population. The incidence has been estimated to be approximately 1-2/100,000 (8,12).

In Southern Italy it ranges from 2.1 to 5.4 x 10⁻⁵ (13). Some studies revealed female preponderance (14,15); other series revealed that it occurred equally in males and females (10,16).

Friedreich's ataxia is characterized by degeneration of the spinocerebellar pathways, the dorsolateral columns, and the dentate nuclei (1). There are few changes in the cerebellar cortex itself (1). The cerebrospinal fluid is usually normal and the CT scan of the brain is either normal or shows mild cerebellar atrophy. The primary clinical signs include ataxia, most marked in the lower limbs and often accompanied by dysarthria, nystagmus is usually present in 70% and skeletal-muscle weakness (17). Optic atrophy and retinal pigmentation is usually present. Pes cavus and scoliosis almost always develop (18). Death is usually sudden and may be secondary to cardiac arrhythmias (17). Cardiac involvement is frequent occurring in some 50% to 90% of cases (19); most commonly concentric hypertrophic cardiomyopathy is found (19,20).

A dilated cardiomyopathy has been noted only rarely (21,22), and congestive heart failure is considered a late complication of the disease. There are suggestions that the increase in catecholamine release may contribute to the development of hypertrophic cardiomyopathy (23). Other authors contest this idea (24).

Multiple studies have shown that the small coronary arteries are abnormal in patients who have cardiac disease and Friedreich's ataxia (25,13). The functional significance of this has been challenged by Hewer (25). Biller, et al. (13) reported a prevalence of 1.5% of cerebral infarction in 131 patients. It occurred in half of the patients who developed atrial fibrillation or atrial flutter with underlying symptomatic cardiomyopathy (13). Speech disorder is common in FA (14).

Some dysarthric symptoms include: Sudden pitch changes (this was present in our patient), ataxic staccato, explosive elements, transient harshness, disturbances of respiratory and articulatory control, bradylalia, and dysdiadochokinesia (26,27).

Electrophysiological and pathological studies suggest that axon degeneration and secondary demyelination occur in peripheral sensory nerves (15).

Disease progression is a question open to discussion. It was suggested (28) that axon loss in the peripheral nerve may increase with age. In contrast, some believe (29) that axon loss does not progress during the disease and that further clinical worsening may result from progressive impairment of the cerebellar and corticospinal pathways (29).

Electrophysiological evaluation of FA patients usually includes determination of motor and sensory conduction velocities (MCV, SCV) and multimodal evoked potentials (30). The degeneration of peripheral sensory and somatosensory pathway

is usually measured by using nerve conduction studies and somatosensory evoked potential (SEPs) and brain-stem auditory evoked potentials (BAEPs) and the blink reflex (30).

Biochemical alterations observed in this disease include a reduced insulin receptor activity which leads to an insulin resistance state and a reduced glucose tolerance in about 40% of patients (31). Several lipid abnormalities have been noted as well, including a striking reduction in linoleic acid (21), low cholesterol levels with a total cholesterol reduction in serum and in the LDL and HDL fractions are described (21). At the cellular level, deficiencies in activity of the pyruvate dehydrogenase complex and alpha ketoglutarate dehydrogenase complex have been described (32).

The results of therapeutic trials in Friedreich's ataxia with a number of drugs, including choline chloride, lecithine, physostigmine, γ -vinyl aminobutyric acid, 5-hydroxytryptophan, benserazide and thyrotropin releasing hormone, have been inconsistent or unconfirmed in terms of producing functional neurologic improvement (2). It was found that the level of the dopamine metabolite, homovanillic acid (HVA) is low in the cerebrospinal fluid (CSF) of patients with either Friedreich's ataxia (FA) or olivopontocerebellar atrophies (31). Amantadine hydrochloride (AH) is known to stimulate dopamine release (34). The use of AH in FA and OPCA was recently tested (35). Both studies revealed an improvement in reaction time (RT) and movement time (MT). Surgery for foot deformity and scoliosis may be of benefit in well selected patients (36). It is essential to minimize perioperative bed rest. So there is no treatment known to influence the slowly deteriorating disease course. In order to minimize disability and prolong ambulation, strengthening and stretching exercises and functional retraining including aerobic endurance exercise are recommended (36).

Early - Onset Cerebellar ataxia with Retained Tendon Reflexes

The other early onset ataxias are listed in Table 3. They are usually rare, with the exception of early onset cerebellar ataxia with retained reflexes, which occurs at a frequency about one quarter of that of FA, is often confused with it, but is genetically distinct. The main clinical difference is that the tendon reflexes are normal or brisk in the disorder (23). It is important to distinguish between these two disorders, since the prognosis is better in the former, with patients losing the ability to walk on average 13 years later than in FA. In addition, severe skeletal deformity, heart disease, and diabetes do not occur (24).

Cerebellar Ataxia with Hypogonadism

The association of progressive ataxia with hypogonadotropic hypogonadism is rare (2). Neurological symptoms usually develop in the third decade and hypogonadism is obvious at puberty. Neurological syndromes include dysarthria, nystagmus, progressive limb and gait ataxia, mental retardation, dementia deafness, choreoathetosis, retinopathy and sensory loss.

Cerebellar Ataxia with myoclonus

The association of cerebellar ataxia and myoclonus, is often referred to as the Ramsay Hunt syndrome. This is a very heter-

Table 3. EARLY - ONSET ATAXIC DISORDERS OF UNKNOWN ETIOLOGY**Friedreich's ataxia****Early-onset cerebellar ataxia with**

Retained tendon reflexes

Hypogonadism

Myoclonus (idiopathic Ramsay Hunt syndrome, progressive myoclonic ataxia)

Pigmentary retinopathy

optic atrophy + or - mental retardation

cataract and mental retardation (Marinesco-Sjogren syndrome)

Deafness

Extrapyramidal features

X-linked recessive spinocerebellar ataxia

TABLE 4: LATE-ONSET ATAXIC DISORDERS OF UNKNOWN ETIOLOGY**Autosomal dominant cerebellar ataxia (ADCA) with**

Ophthalmoplegia, dementia, optic atrophy, extrapyramidal features and amyotrophy may include Machado- Joseph disease) (ADCA type I)

ADCA with pigmentary retinopathy +/- Ophthalmoplegia and extrapyramidal features (ADCA type II)**Pure ADCA of later onset (after age 50) (ADCA type III)****Periodic ADCA****Other syndromes**

ogenous entity. Some of the identifiable causes include Baltic myoclonus, mitochondrial encephalomyopathy, and sialidosis (24). The rest of cases can be labelled as progressive myoclonic ataxia (24). Symptoms include the development of stimulus - sensitive myoclonus or generalized seizures at the end of the first decade of life. Ataxia and dysarthria develop a few years later with pyramidal signs in the limb. The myoclonic part of this syndrome may respond to clonazepam or valproate sodium with marked improvement in motor function.

B. Late Onset Cerebellar Ataxia

These disorders have proved the most difficult and controversial in terms of classification (Table 4). The pathological findings are heterogenous reflecting huge clinical variations in the dominant ataxia (2).

Autosomal Dominant Cerebellar Ataxia Type I (ADCA Type I).

The age of onset of symptoms in this syndrome ranges from 15 to 65 years but is most commonly in the third or fourth decade of life. Ataxia of gait is the most frequent presenting symptom; it usually involves the limbs and is invariably associated with dysarthria. Early onset usually predicts more progressive disability (37). Associated symptoms may include ophthalmoplegia, nystagmus, lid retraction and optic atrophy. Bulbar

symptoms are common during the later stages of disorder and predispose the patient to respiratory infection. Other common symptoms include dementia, extrapyramidal signs, wasting and fasciculation of the face and tongue.

Autosomal dominant cerebellar ataxia Type II (ADCA Type II).

This is clinically and genetically different from ADCA type I. It is characterized in all families having retinopathy. The age at onset is earlier than that of ADCA type I, most commonly occurring between 15 and 35 (2,38).

Autosomal Dominant Cerebellar Ataxia Type III

This is relatively pure cerebellar syndrome in which dementia, ocular or extrapyramidal features do not occur and onset of symptoms usually after the age of 50 years (39). Nystagmus and pyramidal signs in the limbs are quite common.

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